

Evidence Report:

Risk of Cardiac Rhythm Problems During Spaceflight

**Human Research Program
Human Health Countermeasures Element**

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National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

CURRENT CONTRIBUTING AUTHORS

Stuart M. C. Lee	KBRwyle, Houston, TX
Michael B. Stenger	NASA Johnson Space Center, Houston, TX
Steven S. Laurie	KBRwyle, Houston, TX
Brandon R. Macias	KBRwyle, Houston, TX

PREVIOUS CONTRIBUTING AUTHORS

Steven H. Platts	NASA Johnson Space Center, Houston, TX
Michael B. Stenger	Wyle Labs, Houston, TX
Tiffany Phillips	Wyle Labs, Houston, TX
Angela Brown	MEI Technologies, Houston, TX
Natalia Arzeno	Wyle Labs, Houston, TX
Benjamin Levine	Institute for Exercise and Environmental Medicine, Dallas, TX
Richard Summers	University of Mississippi Medical Center, Jackson, MS

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I. PRD RISK TITLE: RISK OF CARDIAC RHYTHM PROBLEMS

Description: Heart rhythm disturbances have been observed in some astronauts and cosmonauts during spaceflight, but it is not clear whether these arrhythmias result from pre-existing conditions or effects of spaceflight. It is hoped that advancements in screening for cardiovascular disease have greatly mitigated this risk. Other heart rhythm problems, such as atrial fibrillation, can develop in crewmembers with normal aging and require periodic screening. There have been suggestions that some spaceflight-related factors may contribute to or hasten the development of these arrhythmias.

II. EXECUTIVE SUMMARY

NASA has concerns regarding the incidence and clinical significance of cardiac arrhythmias that could occur during long-term exposure to the spaceflight environment, such as on the International Space Station (ISS) or during a prolonged (e.g., up to 3 years) sojourn to Mars or on the Moon. There have been some anecdotal reports and a few documented cases of cardiac arrhythmias in space, including one documented episode of non-sustained ventricular tachycardia. The potential catastrophic nature of a sudden cardiac death in the remote space environment has led to concerns from the early days of the space program that spaceflight might be arrhythmogenic. Indeed, there are known and well-defined changes in the cardiovascular system with spaceflight: a) plasma volume is reduced, b) left ventricular mass is decreased, and c) the autonomic nervous system adapts to the weightless environment. Combined, these physiologic adaptations suggest that changes in cardiac structure and neuro-humoral environment during spaceflight could alter electrical conduction, although the evidence supporting this contention consists mostly of minor changes in QT interval (the time between the start of the Q wave and the end of the T wave on an electrocardiogram tracing) in a small number of astronauts after long-duration spaceflight. Concurrent with efforts by NASA Medical Operations to refine and improve screening techniques relevant to arrhythmias and cardiovascular disease, as NASA enters the era of exploration-class missions it will be critical to determine with the highest degree of certainty whether spaceflight by itself alters cardiac structure and function sufficiently to increase the risk of arrhythmias.

III. INTRODUCTION

Some have postulated that the incidence and severity of cardiac arrhythmias would increase as the number and duration of spaceflights increased (Leguay and Seigneuric 1981; Atkov and Bednenko 1992). At present, however, there is little evidence suggesting that cardiovascular adaptation to weightlessness or other spaceflight factors increases astronauts' susceptibility to life threatening arrhythmias. From a clinical perspective, according to the "biological model" of sudden cardiac death (Myerburg et al. 1989), both the substrate and the trigger for arrhythmias should be considered to determine whether long-term spaceflight could lead to an increased risk of sudden death. In this model, structural abnormalities interact with functional alterations, such as electrolyte disturbances, or neuro-humoral modulation, to create an environment in which arrhythmias can be initiated and/or sustained. In patients with coronary artery disease, the substrate is clear: a myocardial infarction (MI) and/or scar leading to focal areas of slowed conduction, a necessary condition for reentry of the electrical impulse. For patients with apparently normal ventricular function, the potential substrate is less

certain. In fact, reentry often is not the mechanism of arrhythmia development in these clinical cases: the arrhythmias may be caused by delayed after-depolarizations, and the triggered activity may be mediated via catecholamines (Lerman et al. 1996). The published report of non-sustained ventricular tachycardia during prolonged spaceflight (Fritsch-Yelle et al. 1998) supports this hypothesis, in that initiation of tachycardia by a late diastolic premature ventricular contraction (PVC) is more consistent with triggered activity than it is with reentry.

There are no definitive data showing that spaceflight is associated with increased frequency or complexity of cardiac arrhythmias, but observational data have been documented that by themselves might suggest that arrhythmias are more prevalent during long flights. There were few reported arrhythmias during early NASA spaceflight programs (Berry 1968; Charles et al. 1996), with the exception of a 22-beat nodal bigeminal rhythm, which was followed by atrial premature beats, during a lunar EVA (Rossum et al. 1997). Holter monitoring performed during 4-16 day Space Shuttle missions revealed the frequencies of arrhythmias during either intravehicular or extravehicular operations (EVA) were virtually the same as frequencies measured before flight (Fritsch-Yelle et al. 1996a; Rossum et al. 1997). Indeed, in these studies, the frequency of arrhythmias may actually have been reduced in flight, although the investigators did not quantify the day-to-day variability of these arrhythmias which is known to be quite wide. However, during Skylab missions (28-84 days), all 9 crewmembers exhibited some form of rhythm disturbance. Most of these rhythm disturbances consisted of single PVCs that were clinically insignificant. Additionally, one crewmember experienced a 5-beat run of ventricular tachycardia during a lower body negative pressure (LBNP) protocol, and another crewmember had periods of “wandering supraventricular pacemaker” during rest and following exercise. Also, PVCs were detected aboard the Mir space station that were not present before flight (Goldberger et al. 1994), and a 14-beat run of ventricular tachycardia was documented (Fritsch-Yelle et al. 1998) (**Figure 1**).

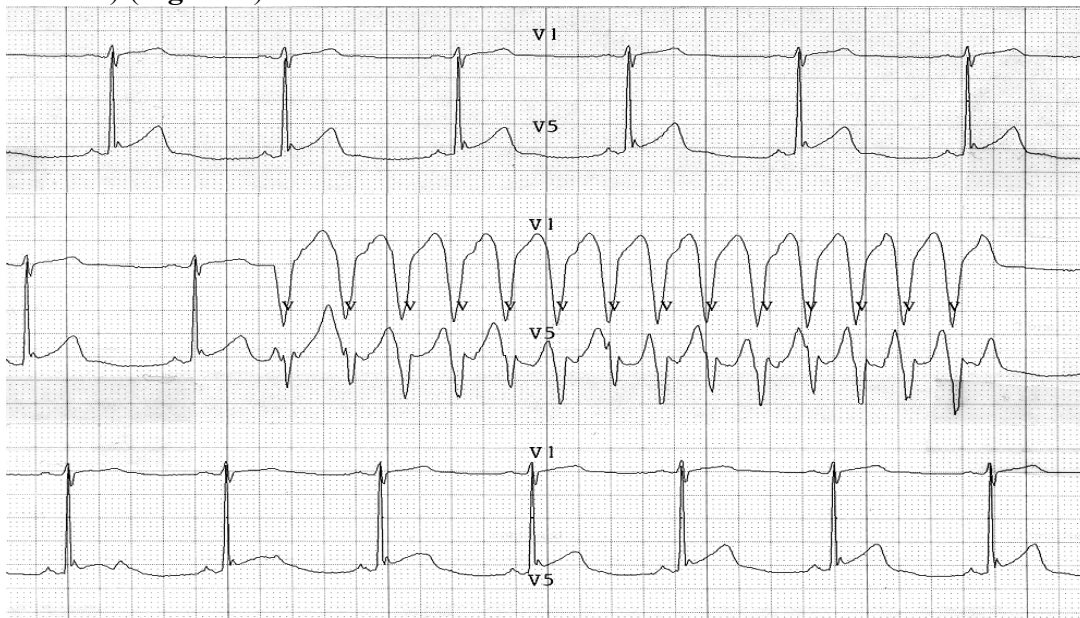


Figure 1. A non-sustained tachycardia recorded in a Mir crewmember (Fritsch-Yelle et al. 1998).

The potential for an increased incidence of arrhythmias during spaceflight might be inferred from crewmember-specific factors (e.g., age, sex) and spaceflight-related adaptations (e.g., fluid shifts, electrolyte disturbances). For example, after long-duration missions corrected QT intervals (QTc), a marker of ventricular repolarization, are slightly prolonged in crewmembers who did not have prolonged QTc intervals after their short-duration Space Shuttle flights (D'Aunno et al. 2003). Unfortunately, Holter monitoring was not performed during these spaceflights; thus, it is not known whether this prolongation was associated with any arrhythmias. Additionally, several investigators have reported that astronauts have decreased left ventricular mass after spaceflight (Perhonen et al. 2001; Summers et al. 2007). Additional potential contributors to this risk are discussed in detail below.

All of these findings raise the concern that cardiac rhythm disturbances may become an issue during the long in-flight tours of duty planned on ISS and future exploration missions; several 1-year ISS missions are being planned, and Mars missions will last approximately 3 years. The degree to which spaceflight and its many variables can be considered arrhythmogenic is not clear, but a serious cardiac rhythm disturbance could have significant impacts on both the spaceflight mission and the long-term health of astronauts and cosmonauts.

IV. EVIDENCE

A. Spaceflight Evidence

Early space program objectives were directed towards launching humans successfully into space and safely returning them home, while gaining an appreciation of the physiological responses to spaceflight (Berry 1968). The human body is evolutionarily adapted to survive in a 1 g gravitational environment (Romero et al. 2015); thus, physiological functions in weightlessness could not be predicted with certainty. To monitor cardiovascular health and function, electrocardiogram (ECG) monitoring of astronauts and cosmonauts was routine practice in early spaceflight missions, but became less frequent as experience was gained with the novel environment of weightlessness and no emergent cardiovascular events were observed (Charles et al. 1996). In later flights, continuous ECG recordings were performed as part of a science experiment, during mission events that might be particularly stressful to the cardiovascular system (e.g., launch, landing, extravehicular activities [EVA]) or during the performance of potentially provocative countermeasures (e.g., exercise, LBNP). Thus, evidence of arrhythmias during spaceflight largely has been anecdotal or observational, although a few systematic studies have been conducted. As a result, ascribing the appearance of arrhythmias during spaceflight to the spaceflight exposure has been difficult. **Table 1** includes an overall summary of currently published reports (5).

Table 1. Summary of reported arrhythmias by flight phase. Adapted from Charles et al. (1996) with supplemental information from others (Berry 1968; Fritsch-Yelle et al. 1998; Gontcharov et al. 2005; Grigoriev et al. 2009). Results are from published reports. PAC: premature atrial contraction. PVC: premature ventricular contraction.

Program	During Launch	During Flight	During EVA	During Reentry or Landing	After Flight
Mercury	Rare PACs, PVCs during pre-launch activities	More pronounced sinus dysrhythmia. One PAC, one PVC, one fusion beat	No EVAs performed		
Gemini		Rare PACs, PVCs (Berry 1968)			
Apollo		On Lunar surface: PVCs, PACs during normal flight, sleep and awakening, and after return to Lunar surface	Lunar surface EVA: atrial bigeminal rhythm with extreme fatigue		
Skylab		PVCs during normal flight and exercise; AV block during LBNP recovery; ectopic beats during LBNP; AV junctional rhythm at rest and during LBNP; ST segment and T-wave changes during maximum stress; ventricular couplet, 3-beat ventricular tachycardia during exercise			Ventricular tachycardia
Space Shuttle	PVCs, PACs	PVCs, PACs (Fritsch-Yelle et al. 1996a)	PVCs, PACs, sustained ventricular bigeminy, blocked P-waves	PVCs, PACs	
Mir	PACs, PVCs (Gontcharov et al. 2005; Kotovskaia and Vil'-Villiams 2007)	PACs, PVCs during rest and exercise (Gontcharov et al. 2005). One evacuation due to arrhythmia (Bogomolov et al. 2009). 14-beat run of ventricular tachycardia (Fritsch-Yelle et al. 1998)	PACs, PVCs (Gontcharov et al. 2005)		
ISS	Not reported	Not reported	Not reported	Not reported	Not reported

1. NASA Spaceflight Experience

Leguay and Seigneuric (Leguay and Seigneuric 1981) compiled some of the reports from the pre-Shuttle era of human spaceflight. At the time, various arrhythmias had been observed during spaceflight, but in general there had been no adverse consequences. With the exception of the Lunar Module Pilot on Apollo 15, little attention had been paid to these events.

The Mercury Program consisted of 6 single-person flights, with durations as short as 15 minutes and as long as 34 hours, with the first mission occurring in May 1961 and the final mission completed in May 1963 (Berry 1968). The Gemini Program encompassed 10 spaceflights from March 1965 to November 1966 (Berry 1968). Two astronauts participated in each flight; the shortest mission was just under 5 hours and the longest was almost 4 days. Six of the missions included EVA. The first EVA was performed on Gemini IV and lasted just 36 minutes; the longest EVA was performed on the final mission of the Gemini Program and was 5.5 hours long. There were no reports of significant arrhythmias during these missions (Anzai et al. 2014).

The Apollo Program, NASA's third human spaceflight program, consisted of 11 3-man missions between 1968 (Apollo 7) and 1972 (Apollo 17) with the specific goal of landing humans on the Moon. Nine of the missions carried humans beyond low Earth orbit, and of these, 6 missions landed on the Moon. Each lunar landing mission, beginning with Apollo 11, also included EVAs, with each successive mission incorporating longer and more complex mission objectives. It was in the course of the Apollo program that the first clinically significant arrhythmia was reported (Anzai et al. 2014). One crewmember during Apollo 15 experienced a 22-beat nodal bigeminal rhythm, which was followed by atrial premature beats (Rossum et al. 1997). This crewmember reported extreme fatigue during the incident, but only reported the incident when questioned by crew surgeons; thus, it was not severe enough to impact the mission. Twenty-one months later the crewmember suffered from coronary artery disease and a cardiac infarction (Leguay and Seigneuric 1981).

Skylab was NASA's first space station; it was visited by 3 separate 3-man crews between May 1973 and February 1974 with mission lengths of 28, 59, and 84 days. During the Skylab missions, several instances of ventricular PVCs, supraventricular PVCs, and nodal arrhythmia were recorded. The arrhythmias occurred during effort tests, EVAs, LBNP sessions, and throughout the entire mission. These included 2 consecutive PVCs when an astronaut was exercising and an episode of atrioventricular dissociation preceded by sinus bradycardia in 2 astronauts (Leguay and Seigneuric 1981).

One hundred thirty-five Space Shuttle missions occurred over the course of 30 years between April 12, 1981 and July 8, 2011, beginning with Space Transportation System (STS) 1 and ending with STS-135. During the first 4 flights (called test flights), ECG was monitored continuously, and frequent PVCs were observed in 2 crewmembers during reentry and landing (Charles et al. 1996). In subsequent missions routine ECG monitoring was conducted only during EVA. According to Charles et al (Charles et al. 1996), one third of the astronauts who flew before 1996 experienced either PACs or PVCs while participating in EVA. Notable ECG findings during EVA were reported in 2 crewmembers: one with 10 minutes of sustained ventricular bigeminy and the other with episodes of frequent PACs.

Two studies of cardiac rhythm disturbances were performed in response to medical reports of arrhythmias occurring in 9 of 14 Shuttle EVA astronauts between 1983 and 1985. Rossum et al. (Rossum et al. 1997) reviewed 24-hour Holter recordings acquired during and after high altitude chamber training, underwater training for EVA (Weightless Environment Training Facility; WETF), 30 days before launch, during and after each EVA, and on return to Earth. The investigators observed no change in the number of PVCs or PACs per hour during flight compared to preflight or postflight (**Figure 2**). Fritsch-Yelle et al. collected 24-hour Holter recordings from 12 astronauts before, during, and after 6 Space Shuttle missions lasting 5-10 days (Fritsch-Yelle et al. 1996a). There was a significant decrease in the number of PVCs per hour and a trend toward a decrease in the number of PACs per hour compared to preflight. In this report no results for individual astronauts were discussed, and some astronauts experienced no dysrhythmias throughout the study.

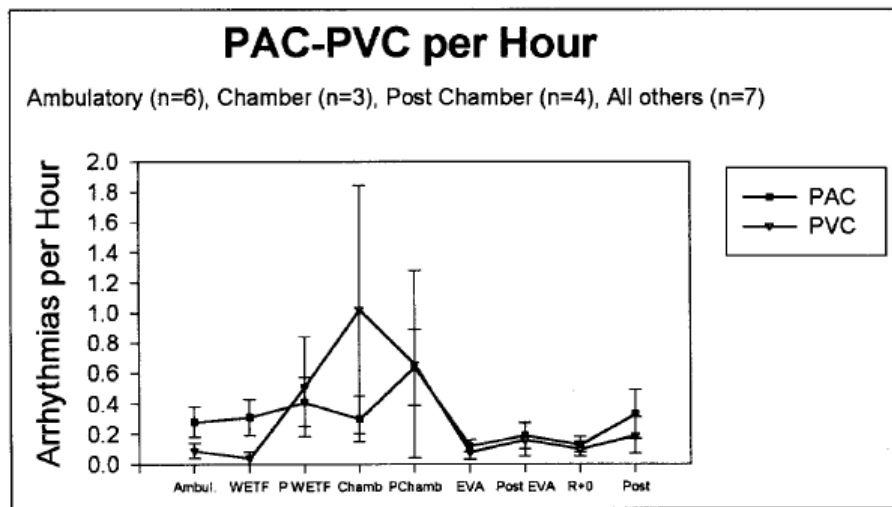


Figure 2. Number of premature atrial (PAC) and ventricular (PVC) contractions before, during and after Space Shuttle flights (Rossum et al. 1997).

In the NASA-Mir program, in which 7 NASA astronauts participated in missions with 12 Russian cosmonauts, ECG monitoring revealed episodic arrhythmias in 10 of the 19 crewmembers, with a range of incidence across crewmembers (Gontcharov et al. 2005). Atrial and ventricular arrhythmias were observed when crewmembers were at rest, exercising, and performing EVA. Arrhythmias also were observed in the same crewmembers during preflight training. In-flight Holter monitoring recorded an isolated incident of a non-sustained 14-beat ventricular tachycardia in one of the crewmember (**Figure 1**), with a maximum heart rate of 215 beats per minute (Fritsch-Yelle et al. 1998). This cosmonaut experienced a single occurrence of a similar event during a previous mission (Gontcharov et al. 2005). Although not part of a systematic scientific study, this case provided evidence of arrhythmias during long-duration spaceflight (Baevsky et al. 2007).

The ISS has been continuously inhabited since the arrival of Expedition 1 on November 2, 2000. Crews have consisted of as few as 2 and as many as 6 astronauts and cosmonauts. One of the specific aims of the Integrated Cardiovascular Study (Principal

Investigators: Benjamin Levine, University of Texas, Southwestern Medical Center, and Michael Bungo, University of Texas Health Science Center) was to investigate the number of arrhythmias occurring in ISS astronauts using 24-h Holter recordings obtained before, during, and after the mission. These results have yet to be published, but preliminary results presented in the final report to NASA suggest that the majority of astronauts participating in these long-duration missions did not have an increase in the number of arrhythmias, although 2 of the 13 participants did have increased frequency of arrhythmias (Levine and Bungo 2015). One crewmember had a substantial increase in the number of supraventricular arrhythmias, and another crewmember experienced an increase in ventricular arrhythmias. The investigators have suggested that there may be a subset of individuals who may be more susceptible to an increased incidence of arrhythmias, but no data yet are available to substantiate this claim or to suggest a validated mechanism. A key objective for future exploration missions may be to identify the phenotype and the stressors that could be responsible for the increases in arrhythmias that occur in certain individuals (Romero et al. 2015). Unfortunately, no continuous ECG data were collected from the 2 ISS astronauts who were on-orbit for 340 days in 2016 and 2017, which could have provided more recent data regarding stays in weightlessness similar to durations expected to be required for a mission to Mars.

2. Soviet and Russian Experience

A large amount of Soviet-era spaceflight results, including human research data, have not been published or observations widely disseminated (Bogomolov et al. 2009). Until the Apollo-Soyuz Test Project, space medicine practices at NASA and in the Soviet (later Russian) space programs developed independently. Cooperation and exchange of information between the two space programs manifested as the U.S.-USSR Joint Working Group on Biology and Medicine in the early 1970s and the NASA and Russian space programs jointly prepared for the NASA-Mir Program in the early 1990s. A 1992 agreement between the U.S. and the Russian Federation paved the way for a series of joint spaceflight missions from 1994 to 1998 (Bogomolov et al. 2009). Joint missions included 7 Russian cosmonauts participating in Space Shuttle missions and 7 NASA astronauts participating in long-duration missions on the Mir Space Station.

Romanov et al. (Romanov et al. 1987) reviewed electrophysiology results from Soviet and Russian spaceflight missions between 1964 and 1985 and reported observations of supraventricular and ventricular premature beats, with the highest reported frequency occurring during launch and the first hours of the mission. Whereas most in-flight arrhythmias have been considered not to be clinically significant, one cosmonaut returned before the planned end of his mission because of persistent supraventricular tachycardia (Bogomolov et al. 2009). ECG changes that were observed after these missions generally resolved during re-adaptation phase, but 3 cosmonauts later demonstrated ECG consistent with ischemic heart disease (Romanov et al. 1987). In a separate study, cosmonauts who completed a one-year mission on the Mir Space Station participated in a 24-h Holter data collection in the first 24 h after landing. Each cosmonaut had infrequent episodes of isolated ventricular extrasystole (Grigoriev et al. 1991).

It is unknown whether long-duration exposure to weightlessness itself may precipitate cardiac arrhythmias. Based on observations and clinical judgment medical operations

personnel have suggested that some of these incidents may have been related to pre-existing, undiagnosed coronary artery disease. Additional pre-selection tests to screen astronauts and cosmonauts before selection and flight assignments, including coronary artery calcium scoring, have been added to reduce such occurrences in the future.

3. Launch and Landing

Launching into and landing from space are significant physical and psychological stressors that historically were significant sources of concern for the development of arrhythmias. It has been common practice for NASA and the Soviet/Russian spaceflight programs to monitor the crewmembers' ECG. Kotovskaia et al. (Kotovskaia and Vil'-Villiams 2007) reported that individuals who exhibited arrhythmias in the preflight period also had similar arrhythmias during launch and entry into weightlessness. Kotovskaia et al. (Kotovskaia and Vil'-Villiams 2007) compared ECG data from non-professional cosmonaut visitors (29-60 years old) and medically-qualified cosmonauts (31-49 years old) that were obtained during reentry on the Soyuz spacecraft after short-duration stays on ISS (8-12 d). The non-professional flyers, particularly the older ISS visitors, had higher heart rates and more frequent arrhythmias than the cosmonauts. Less rigorous medical screening for nonprofessional space visitors may have contributed to this disparity.

Perez et al. (Perez et al. 2003) trained 34 Space Shuttle astronauts to instrument themselves with continuous ECG for the measurements of heart rate and with a brachial cuff for automated blood pressure measurements. Measurements were obtained before flight, and astronauts donned the instrumentation while on-orbit to obtain data during reentry and immediately after landing. The primary objective of this study was to determine the effectiveness of the anti-gravity suit (g-suit), and thus no specific analyses for arrhythmias were performed.

Tests have been conducted to assess ISS crewmembers' ability to complete simulated exploration mission-specific tasks soon after landing. These data are still being collected and analyzed. There were no specific analyses for arrhythmias during testing after Space Shuttle missions, but clearly some arrhythmias were present in those participants. The authors reported that they ignored the influence of ectopic beats (removed them from the Holter files) in their analysis of heart rate and autonomic function (Arzeno et al. 2013). The nature and frequency of these arrhythmias were not described.

An understudied aspect of the arrhythmia risk is whether individuals who experience more frequent arrhythmias during spaceflight recover (have fewer arrhythmias) after the mission, and what is the time course of this recovery. This is an important element of our understanding of the long-term health risks associated with spaceflight; this aspect may influence the health care and treatment of astronauts in the future (Romero et al. 2015).

4. Exercise

No specific flight rules exist to discourage strenuous exercise countermeasures during short- or long-duration spaceflight; in fact, high-intensity, interval exercise, characterized by periods of near maximal, maximal, and supramaximal efforts alternating with low-intensity efforts, have been prescribed for astronauts in the Space Shuttle, Mir, and ISS programs (Siconolfi et al. 1994; Hayes et al. 2013; Loehr et al. 2015; Kozlovskaya et al.

2015) because of the demonstrated efficacy of these exercises in spaceflight analogs (Greenleaf et al. 1989; Lee et al. 2007, 2009; Hastings et al. 2012). Heart rhythm is not monitored by ECG during routine exercise before, during, or after spaceflight (Moore et al. 2010), and therefore arrhythmias are not detected except during clinical tests. ISS astronauts are encouraged to wear heart rate sensors to monitor exercise intensity and log exercise sessions for medical and research purposes, although this is not a strict requirement. Careful evaluation of heart rate logs could be used to screen for abnormal R-R intervals, but confirmation of arrhythmias would require ECG monitoring.

Because of concerns about increasing frequency of arrhythmias and S-T segment changes during high intensity exercise, NASA historically has limited exercise testing for medical and research objectives to work rates less than or equal to 85% of preflight maximal oxygen consumption (Trappe et al. 2006; Moore et al. 2010), except in specific, well-controlled cases. Routine exercise tests on NASA vehicles generally have been submaximal, and similar constraints on exercise tests are employed in Russian missions, particularly during the first week of a mission (Kozlovskaya et al. 1995) and after landing (Fortney et al. 1998). During early ISS missions, NASA astronauts participated in monthly submaximal exercise tests, consisting of 5 minutes of rest followed by three 5-minute stages of exercise at work rates equivalent to 25%, 50%, and 75% of preflight maximal aerobic capacity. In a review of 26 of these exercise tests, Hamilton et al. reported no arrhythmias or S-T segment changes (Hamilton et al. 2005). Although not specifically reported, no research studies to-date have indicated that exercise tests to maximal exertion were terminated due to arrhythmias before, during, or after short- (Siconolfi et al. 1994; Levine et al. 1996; Moore et al. 2001; Trappe et al. 2006) or long-duration spaceflight (Moore et al. 2014, 2015). Similarly, there were no reports of arrhythmias leading to test termination during submaximal exercise tests before, during, or after short- (Rummel et al. 1973; Rummell et al. 1975) and long-duration missions (Moore et al. 2015). That no arrhythmias occurred cannot be discerned from this reporting though as that analysis was not the specific objective of these studies.

Astronauts and cosmonauts routinely participate in a postflight reconditioning program, typically during the first 45 days after landing (Kozlovskaya et al. 1995; Loehr et al. 2015; Kozlovskaya et al. 2015). Typically, ECG monitoring is not performed during these reconditioning sessions, and therefore identification of arrhythmias is not possible.

5. Lower Body Negative Pressure

During the Apollo Program, Hoffler et al. (Hoffler et al. 1974; Hoffler and Johnson 1975) used LBNP or stand tests to measure orthostatic tolerance in 24 male astronauts before and after exposure to weightlessness. Although decreased orthostatic tolerance was inferred from higher heart rates during these stressors, no significant arrhythmias were reported. During the Skylab Program, supraventricular and ventricular beats were observed in all crewmembers (Charles et al. 1996). Ectopic beats were more frequently observed during greater levels of LBNP, although they also were noted at rest (Hoffler et al. 1977). Atrio-ventricular junctional rhythms also were seen in some crewmembers. As reported by Hoffler et al. (1977), arrhythmias that occurred during the Skylab LBNP tests were considered clinically significant.

All Russian crewmembers participate in LBNP countermeasures sessions in the 3 weeks before landing from a long-duration spaceflight. This simulates the fluid shifts and

cardiovascular stresses associated with standing in normal gravity (Wolthuis et al. 1974) as well as stimulating support areas on the soles of the feet (Kozlovskaya et al. 1995, 2015). A Russian flight surgeon is available on console to monitor the crewmembers' ECG and blood pressure in real time. The protocol used for this countermeasure was developed from a series of bed rest studies, in which subjects were placed in a head-down tilt position for 14 to 182 days (Kozlovskaya et al. 1995).

6. Ground-Based Prevalence of Atrial Arrhythmias

Prior to 2010, 17 astronauts had presented with atrial arrhythmias out of a total cohort of 317 active and retired astronauts, which represents a prevalence of approximately 5% (Barr 2010). No arrhythmias were recorded during flight, and most cases were asymptomatic. Of these, 5 individuals presented with atrial arrhythmias between 2001 and 2010 and received radiofrequency ablation treatment. This prevalence of atrial fibrillation is not substantially different from rates reported for the general population (Abdulla and Nielsen 2009); however, because of more recent cases NASA organized and convened the Atrial Arrhythmia Summit on January 22, 2010, to solicit expert opinion (Barr 2010). Summit panel members and attendees, experts in the fields of electrophysiology, cardiology, aerospace medicine, and epidemiology, were given the charge of reviewing cases of atrial arrhythmias in astronauts with the intent of providing recommendations regarding screening, diagnosis, and treatment of the astronaut corps; determining lifestyle and spaceflight-related factors that might predispose astronauts to atrial arrhythmias; and assessing risks to astronauts who participate in long-duration spaceflight or extravehicular activities after treatment.

While the prevalence of atrial arrhythmias was not stated as a significant concern, the age of presentation was lower in astronauts than in the general population (~40 vs. ~60 years old (Abdulla and Nielsen 2009) (Barr 2010). The panel suggested two factors that could account for earlier than expected presentation of atrial arrhythmias: more frequent and comprehensive screenings in the astronaut corps in the form of annual physicals leading to a higher discovery rate; and greater levels of vagal tone associated with a high frequency and duration of aerobic exercise performed by astronauts (Wilhelm 2014). Although exercise is not rigorously controlled or prescribed for astronauts when they are not in space, when NASA astronauts are assigned to an ISS mission they specifically are allotted 4 hours of preflight exercise training in their weekly preflight schedule, and they work directly with the Astronaut Strength, Conditioning, and Rehabilitation specialists (ASCRs) (Loehr et al. 2015); astronauts who are not in the preflight training program are encouraged to maintain regular exercise habits. In middle-aged non-elite distance runners of similar age range as the average astronauts (40-50 years old) lifetime training volume is associated with increased vagal tone, prolongation of signal-averaged P-wave duration, and an increase in left atrial volume (Wilhelm et al. 2011a). Adaptations such as these, coupled with a higher systolic blood pressure, are more pronounced in men than women and may explain the different rates of atrial fibrillation associated with sex (Wilhelm et al. 2011b). Other investigators have noted an association between exercise volume and risk of atrial fibrillation in men but not in women (Zhu et al. 2016).

In general, astronauts are perceived to be fitter than the general population. For 30 male and 7 female astronauts who participated in preflight cycle ergometry testing to maximal exertion before their mission in the first 10 years of the ISS program

(Expeditions 1-25), the average aerobic capacity was 44 ± 8 and 41 ± 7 ml/kg/min, respectively (Moore et al. 2015). With an average age of 46 ± 4 and 43 ± 3 years in these men and women, respectively, the average crewmember's aerobic capacity represents percentile ranking of $\sim 60^{\text{th}}$ in men and $>80^{\text{th}}$ in women (American College of Sports Medicine 2013). Similarly, moderate to high levels of aerobic fitness were observed in 9 men and 5 women astronauts who participated in Expeditions 19 through 33; their average aerobic capacity was ~ 41 ml/kg/min, and their average age was 49 years (Moore et al. 2014). These values are within the same range as previously reported data from 3 studies conducted in Space Shuttle astronauts, in which the mean preflight aerobic capacity across studies ranged from 38 to 48 ml/kg/min in a total of 15 men and 3 women (Levine et al. 1996; Moore et al. 2001; Trappe et al. 2006).

While the Atrial Arrhythmia Summit panel concluded that there was no evidence that spaceflight-related factors contribute to the development of atrial arrhythmias during spaceflight, they speculated as to which specific factors might be of concern: weightlessness-induced cephalad fluid shifts resulting in atrial distension; spaceflight-induced increase in sympathetic activation; plasma volume expansion secondary to elevated dietary sodium intake in salt-sensitive individuals due to the use of sodium as a food preservative for spaceflight missions; and chronic radiation exposure.

B. Ground-Based Evidence

In general, bed rest subjects do not exhibit increases in ventricular ectopy, although one study has suggested a potential for increased susceptibility based on microvolt T-wave alternans (MTWA) assessed during a graded exercise test. After 9 to 16 days of bed rest, the number of subjects who were MTWA positive increased from 17% (4 of 24) before bed rest to 42% (10 of 24) after bed rest (Grenon et al. 2005); 2 of the 4 subjects who were categorized as MTWA positive before bed rest became MTWA negative, while 8 who were negative before bed rest were categorized as MTWA positive after bed rest. However, MTWA was not present in any subject who had a heart rate below 110 bpm, the threshold for which MTWA would be considered clinically significant. Clinically significant MTWA is associated with cardiac arrest, sudden death, and ventricular arrhythmias in patient populations (Rosenbaum et al. 1994; Ikeda et al. 2002).

Numerous studies have shown decreases in left ventricular mass and/or volume during bed rest as an analog of spaceflight (Levine et al. 1997; Perhonen et al. 2001; Arbeille et al. 2001; Dorfman et al. 2007; Westby et al. 2016). Left ventricular mass has been shown to decrease by 8 percent after 6 weeks of bed rest, which was thought to be related to decreased physiological loading (Perhonen et al. 2001). Although decreases in left ventricular mass would be expected to contribute to decreased orthostatic tolerance (Levine et al. 1997) and exercise capacity (Dorfman et al. 2007), to our knowledge no post-bed rest exercise testing has been terminated as a result of arrhythmias (Lee et al. 2010).

Ground-based animal studies have determined the effects of simulated weightlessness on the cardiovascular system. Tachycardia has been observed in standing rats, after hindlimb unloading for 28 days (Ray et al. 2001). Decreased cardiac mass has also been documented in studies of hindlimb-suspended rats (Bao et al. 1999). However, hemodynamics in humans differ from hemodynamics in quadrupeds; thus, the rat is not

the most appropriate model in which to examine weightlessness-induced cardiovascular adaptations (Rowell 1993).

Recently, mice that were hindlimb suspended for 28-56 days were found to have enlarged hearts with decreased contractility as well as an increased susceptibility to pacing-induced arrhythmias as detected by echocardiography (Respress et al. 2014). Further, cardiomyocytes harvested from the tail-suspended animals demonstrated an increased leakiness of calcium from the sarcoplasmic reticulum, as well as increased frequency of spontaneous calcium release that may have been caused by elevated phosphorylation of the ryanodine receptor (RyR2).

C. Contributing Factors

Despite previous reports describing the occurrence of arrhythmias during spaceflight, the notion that exposure to weightlessness is a specific causative factor has been challenged (Convertino and Cooke 2005; Convertino 2009). However, factors associated with crew health as well as adaptation to weightlessness and the spaceflight environment should be considered (Gontcharov et al. 2005).

1. Preflight Condition

The episode of ventricular tachycardia that occurred in one Mir crewmember, while concerning for the crewmember, does not in and of itself provide solid evidence that spaceflight is arrhythmogenic, especially given that previous episodes had been observed in this individual (Convertino and Cooke 2005). During the NASA-Mir Program, all 10 astronauts and cosmonauts who experienced atrial or ventricular arrhythmias during their mission had similar findings during their preflight training, although the episodes were perhaps less frequent or severe before launch (Gontcharov et al. 2005). Further, the crewmember who experienced a run of ventricular tachycardia during his NASA-Mir mission (Fritsch-Yelle et al. 1998) had a similar event during a previous mission, and one crewmember who had S-T segment depression during EVA had similar S-T segment changes before launch (Gontcharov et al. 2005).

A review of ECG records from 30 cosmonauts who participated in long-duration missions (73-197 days in duration) on either Mir or ISS determined that the majority of the crewmembers (70%) did not exhibit arrhythmias during preflight training, launch, or reentry, and a few (10%) who had arrhythmias before flight did not have arrhythmias during launch or landing (Kotovskaia et al. 2008). However, a small number of individuals had increased frequencies of rhythm and conduction disturbances during reentry that were not observed during preflight training.

Data from early spaceflight missions should be interpreted with caution because attitudes toward dietary and cardiovascular health habits have evolved over the history of the space program. For example, individuals who were considered very healthy in the 1960s may have been habitual smokers, whereas fewer astronauts smoke now. Further, cultural attitudes regarding health and wellness differ among international partner countries.

2. Age and Gender

As of 2005, the average age of an individual who was selected for the astronaut corps was 36 and 35 years for men and women, respectively, and the average age of the active

astronauts was 45 and 44 years for men and women, respectively (Hamilton et al. 2005). Thus, most astronauts are “middle-aged” by the time they fly in space, and are likely to experience age-related health effects. Whereas spaceflight crews now include more women than ever (women now constitute ~20% of the current active NASA astronaut corps), the majority of the astronauts and cosmonauts who fly in space are middle-aged men (Harm et al. 2001; Platts et al. 2014), who, because of their age and sex, are more likely to experience dysrhythmias and have subclinical manifestations of cardiovascular disease.

3. Fluid Shifts

Entry into weightlessness causes cephalad fluid shift (Thornton et al. 1977, 1987), which initially results in distension of the cardiac chambers (Buckey et al. 1996; Videbaek and Norsk 1997; Corsi et al. 2002; Caiani et al. 2006) that resolves somewhat (Arbeille et al. 2001) as the body fluids are redistributed and blood and plasma volume decrease (Leach et al. 1996; Meck et al. 2001). That is, although stroke volume and cardiac output initially increase in weightlessness, they return to near preflight standing levels over the first few days of flight (Prisk et al. 1993). Similarly, others have reported no change or a decrease in stroke volume and cardiac output during long-duration spaceflight compared to preflight levels at supine rest (Herault et al. 2000; Hamilton et al. 2011). In contrast, Norsk et al. (Norsk et al. 2015) recently reported that cardiac output and stroke volume after 3 months of weightlessness are increased by more than 30% relative to measurements taken preflight at seated rest. Further, although not a direct measure of atrial distension, internal jugular vein cross-sectional area also is increased during short- and long-duration spaceflight (Herault et al. 2000; Arbeille et al. 2001) and internal jugular venous pressures increased during parabolic flight (Martin et al. 2016). Additionally, a small amount of data from parabolic flight and spaceflight (Summers et al. 2010) and preliminary observations from a recent ISS investigation suggest that the cardiac chambers appear to become more spherical in weightlessness, which might influence cardiac remodeling.

4. Reduced Cardiac Mass

Evidence suggests that apoptosis, or “programmed cell death” occurs in response to pathological, physiological, and/or genetic signals, and this may be a key mechanistic factor in the development of cardiac arrhythmias. For example, apoptosis associated with atrophy and fibro-fatty replacement of right ventricular tissue has been identified as the likely mechanism for arrhythmia development in arrhythmogenic right ventricular dysplasia, a condition that may lead to sudden death in otherwise healthy young individuals (Basso et al. 1996; Mallat et al. 1996).

Indications of reduced cardiac mass as a result of stays in weightlessness were observed in early NASA spaceflight programs. Postflight cardiothoracic ratio, calculated from the posterior/anterior chest X-rays, was reduced in 24 of 30 Apollo astronauts with a mean loss of 5% (Hoffler et al. 1974; Hoffler and Johnson 1975). These data provided only a quantitative measure of the dimensions of the heart as a whole, and therefore it is not possible to determine specific changes in chamber dimensions or myocardial mass with these measures.

Multiple investigators have also reported decreased cardiac mass, particularly in the left ventricle, following chronic exposure to simulated spaceflight (Levine et al. 1997; Perhonen et al. 2001; Spaak et al. 2005; Dorfman et al. 2007; Shibata et al. 2010; Hastings et al. 2012; Carrick-Ranson et al. 2013), with the magnitude of cardiac atrophy associated with the duration of exposure (Westby et al. 2016). Additionally, results from a small number of women suggest that sex does not affect the magnitude or time course of cardiac atrophy (Tuday and Berkowitz 2007; Dorfman et al. 2007; Westby et al. 2016). However, the effects of unloading can be prevented by exercise alone (Shibata et al. 2010; Hastings et al. 2012; Carrick-Ranson et al. 2013) or in combination with orthostatic-like stress (Dorfman et al. 2007).

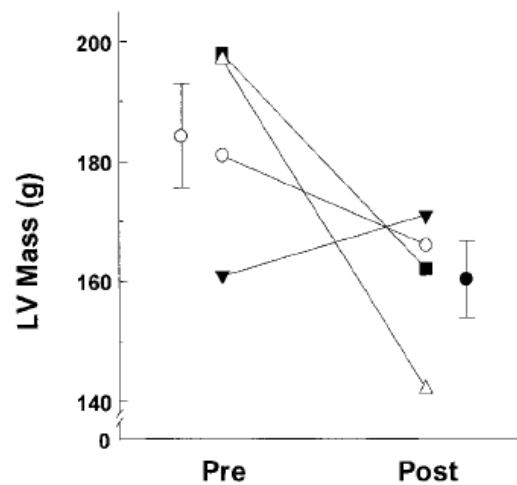


Figure 3. Left ventricular mass measured by magnetic resonance imaging before and after short-duration spaceflight. Lines represent results from individual astronauts (n=4). The average response (mean +/- SD) is represented by circles.

Although most astronauts routinely performed exercise during Space Shuttle missions (Hayes et al. 2013), there are reports of decreased left ventricular mass after short-duration spaceflight. Perhonen et al. (Perhonen et al. 2001) reported that left ventricular mass on average tended to be less following a 10-day Space Shuttle mission (-12%, $p=0.07$), but there was substantial individual variability among these astronauts. Left ventricular mass decreased from pre- to postflight in 3 of 4 astronauts (measured using cardiac magnetic resonance imaging on landing day (Error! Reference source not found.)), but one astronaut experienced an increase in LVM of ~7%. Importantly, this crew performed little to no exercise during the course of their mission other than that required for participation in other experiments. Summers et al. (Summers et al. 2007) used 2-dimensional echocardiography to assess left ventricular mass on landing day after Space Shuttle missions and reported decreases in mass similar to those reported by Perhonen et al. (Perhonen et al. 2001), although full recovery had occurred days after landing (Figure 4).

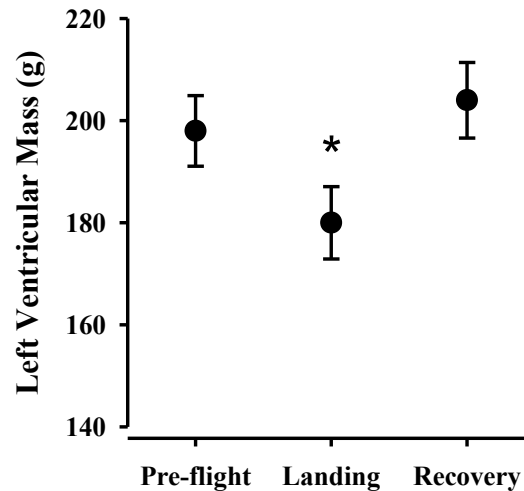


Figure 4. Left ventricular mass before and after short-duration spaceflight (n=38) drawn from Summers et al. 2005. * = $p \leq 0.05$.

Currently no published reports exist regarding the effects of long-duration spaceflight on cardiac mass and volume. Unpublished data (Platts et al., NASA Johnson Space Center, Cardiovascular and Vision Laboratory) suggest decreased left ventricular mass after 4-6 months of spaceflight during the early ISS missions. In these subjects, the reduction in left ventricular mass was double that observed after short flights, and ventricular mass did not fully recover by the third day after landing (**Figure 5**), as had been reported by Summers et al. (Summers et al. 2007) following short-duration missions. It has yet to be reported in the peer-reviewed literature whether these changes persist after exercise countermeasure hardware was improved (Korth 2015) and the intensity of exercise countermeasures was increased (Loehr et al. 2015). However, one of the specific aims of the Integrated Cardiovascular Study (Principal Investigators: Benjamin Levine, University of Texas, Southwestern Medical Center, and Michael Bungo, University of Texas Health Science Center) was to investigate whether cardiovascular mass and volume in ISS astronauts is a contributing factor for cardiac arrhythmias (Levine and Bungo 2015). Preliminary results presented in their final report to NASA indicate that, on average, ventricular mass did not change significantly from pre- to postflight in the 13 astronauts studied, but there was considerable variability in this effect. Pre- to postflight changes in left ventricular mass were directly related to the pre- to in-flight change in cardiac work (calculated from 24-hour recordings of heart rate and finger blood pressure), and it is likely that the largest influence is from varying levels of performance of in-flight exercise countermeasures. Additionally, these investigators noted that there was no evidence of focal scarring or diffuse fibrosis from MRI that might be indicative of cardiac injury.

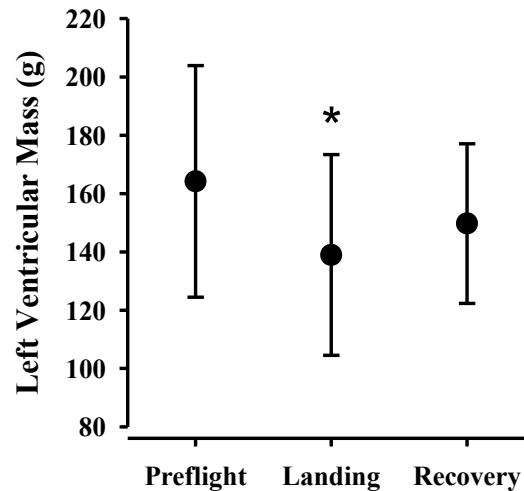


Figure 5. Left ventricular mass before and after long-duration spaceflight (n=6) drawn from unpublished data from Platts et al., NASA Johnson Space Center, Cardiovascular and Vision Laboratory. * = $p \leq 0.05$.

There has been some disagreement over the mechanism that causes decreases in ventricular mass, especially after short-duration missions. Evidence exists that supports the concept that tissue dehydration contributes to the loss in mass after short-duration spaceflights (Perhonen et al. 2001), but this factor likely does not fully explain losses after long-duration missions. However, there are data from bed rest studies showing that the decrease in mass can be prevented with exercise and/or nutritional countermeasures (Dorfman et al. 2007).

5. QT Prolongation

The QT interval is a measure of the combined duration of ventricular depolarization (QRS) and repolarization (T wave). The QRS complex is usually of fixed duration in healthy individuals. Thus, changes in QT duration represent alterations in ventricular repolarization. The QT interval of the surface ECG is a spatial and temporal summation of all cardiac cellular action potentials. Not all cells within the heart share identical action potentials; therefore, a certain degree of variability, or inhomogeneity exists in their repolarization time. The degree of inhomogeneity during repolarization directly correlates with the overall morphology of the QT waveform (primarily the T-wave) and in most cases with the QT interval duration. A clear association between the magnitude of inhomogeneity of repolarization and the risk for the development of ventricular arrhythmias has been established (Lux et al. 2001; El-Sherif 2001; Shusterman et al. 2006).

The QT interval is often corrected for heart rate and is shown as QTc. Some conditions that can prolong the QTc interval are ischemic heart disease, autonomic dysfunction, bradycardia, electrolyte abnormalities, cardiac remodeling, and diuretic medications that interfere with the cardiac potassium ion channels (Ishida et al. 1995; Lo et al. 1996; Savelieva et al. 1999; Haverkamp et al. 2000; Khan 2002). Which of these

factors are seen in long-duration astronauts? First, it is known that astronauts develop changes in the autonomic nervous system (Fritsch et al. 1992; Fritsch-Yelle et al. 1996b; Meck et al. 2001; Rossum et al. 2001). Second, on long-duration flights, astronauts have a relative bradycardia compared to astronauts on short-duration flights (Meck et al. 2001). Third, there is evidence of cardiac remodeling after long-duration flights. Fourth, there are medications available to astronauts aboard the ISS that prolong QTc interval, including ciprofloxacin, haldol, inderal, verapamil, zithromax, Zoloft®, and nortriptyline. The environment created by the combination of factors listed above might cause or exacerbate the prolongation of the QT interval.

Prolongation of QTc interval does not itself guarantee an increase in ventricular arrhythmias. For example, sleep, hypothyroidism, and use of the anti-arrhythmic drug amiodarone all prolong QTc without increasing the incidence of ventricular arrhythmias. It is possible that spaceflight presents a similar situation; however, at this time, the determination cannot be made due to lack of data. The finding of QTc prolongation in astronauts has been of concern from the clinical operations perspective. Such prolongation has been documented on several occasions but it is not clear whether these findings have any clinical significance or portend risk (D'Aunno et al. 2003; Mitchell and Meck 2004).

6. Electrolyte Disturbances

Cardiac rhythm abnormalities and exercise intolerance observed in the Apollo 15 Lunar Module Pilot were attributed at the time to electrolyte disturbances, particularly hypokalemia (Leguay and Seigneuric 1981). Inadequate potassium intake was suspected, and before Apollo 16 a 12-day bed rest study with low potassium intake was conducted with 2 subjects as a simulation of the Apollo 15 mission. The study included replication of the crew's sleep schedule and caloric intake (Hyatt et al. 1975). However, neither of the bed rest subjects developed symptomatic hypokalemia, only one demonstrated minor ECG abnormalities, and the decrease in exercise capacity and orthostatic tolerance in these subjects was no more than expected for a bed rest of similar duration with normal dietary intakes.

Serum and urinary potassium levels decreased by 7% and 47%, respectively, in both Apollo crewmembers (Leach et al. 1975), but a later review of the Apollo 15 mission suggested that magnesium deficiency contributed to the arrhythmias and other symptoms (Rowe 1998). However, data from short- and long-duration spaceflight may not support the contention that chronic low magnesium levels as a significant cardiovascular risk factor during spaceflight. Although their results are not specific to Apollo 15, Smith and Zwart (Smith and Zwart 2015) report that during long-duration ISS missions, urinary magnesium concentrations were elevated within the first 2 weeks of the mission and serum levels were elevated above preflight levels after 3-4 months of flight. Both urinary and serum magnesium decreased and were lower than preflight values on landing day but then returned to preflight levels within 1 month after landing. Despite these dynamics, tissue levels of magnesium, measured in epithelial cells from sublingual scrapes, were not different from preflight values on landing day or 1 month after landing. After short-duration spaceflight, neither urinary nor serum magnesium levels were different from preflight values.

Prolonged QTc intervals observed after long-duration, but not short-duration, spaceflight were not associated with clinically relevant changes in electrolyte levels (D'Aunno et al. 2003). In 5 Shuttle and 7 Mir astronauts, there was no pre- to postflight change in serum magnesium or calcium levels; although serum potassium measured on landing day was significantly less than before flight, the levels were still within clinical normative ranges.

7. Catecholamines

Elevated catecholamines and increased sympathetic activity have been associated with the development of arrhythmias in terrestrial populations (Leguay and Seigneuric 1981). Leach et al. (Leach et al. 1996) reported no change in serum catecholamines from pre- to in-flight and that urinary norepinephrine levels were lower during Space Shuttle missions than before launch. More recently, Norsk et al. (Norsk et al. 2015) reported no change in norepinephrine and epinephrine levels from preflight (seated) to in-flight during 3-6 month ISS missions.

8. Oxidative Stress

A number of studies have suggested that biomarkers of oxidative stress are elevated during spaceflight, although the specific source of the oxidative stress is yet to be determined (Smith et al. 2009). In the course of a spaceflight mission, astronauts can experience oxidative stress that is induced from a variety of conditions, including changes in exercise and dietary habits, exposure to high-linear energy transfer radiation, psychological stress, and hyperoxic conditions associated with EVA and prebreathe protocols that are implemented prior to EVA as a countermeasure for decompression sickness (DCS). A current experiment is measuring vascular structure and function in 13 astronauts who spend 6-12 months on ISS to determine whether these crewmembers exhibit subclinical manifestations of cardiovascular disease and whether a relationship exists between vascular adaptations to spaceflight and biomarkers of oxidative stress and inflammation (Lee et al. 2017). Previous work by others has documented increased carotid intima media thickness (Arbeille et al. 2016) and carotid artery stiffness (Hughson et al. 2016) from before to after long-duration spaceflight. The work by Lee et al. (Lee et al. 2017) is the first to acquire in-flight vascular measures and biomarkers to characterize the time course of spaceflight-induced adaptations as well as to measure the long-term effects on vascular health with measures extending out to 5 years after landing. Given that ionizing radiation is a potent source of oxidative stress and has been associated with cardiovascular disease, even at relatively low doses (Little et al. 2012; Little 2016), this study of astronauts in low Earth orbit also will serve as an important baseline to which to compare findings from astronauts who are exposed to space radiation during future exploration missions. Studying the physiologic and health consequences of different levels of radiation from low Earth orbit and travel beyond the van Allen belts is critical to the understanding of any synergistic effects of radiation and weightlessness and the appreciation of the risks associated to missions to Mars and other destinations.

EVAs typically last between 4 and 8 hours, and require pre-breathing 100% oxygen before the EVA. Acute hyperoxic exposures are associated with increased systemic and coronary artery vasoconstriction, both at rest and during exercise. Vitamin C can reverse

the effects, which supports the hypothesis that these effects are mediated by the formation of reactive oxygen species (Ranadive et al. 2014).

NASA has used prebreathe protocols to lessen the likelihood that astronauts will develop decompression sickness when they move from working in the space vehicle in which atmospheric conditions are maintained similar to that on Earth (~14.7 psi) to the EVA suit. When working in the EVA suit, astronauts must use force to bend the suit at the joints which increases the physical effort and rate of fatigue. The NASA EVA suit, the EVA Mobility Unit, which has been used during the Space Shuttle and ISS programs is pressurized to 4.7 psi, and the Russian Orlan spacesuit is pressurized to 3.5 psi. A variety of prebreathe protocols have been employed by NASA over the years, including Shuttle decompression, camp-out, exercise prebreathe, and 4-hour prebreathe. The objective of the NASA prebreathe research program has been to reduce time required to perform the prebreathe activity while not increasing the likelihood of DCS. In addition to increasing the duration of exposure to a hyperoxic environment, a longer prebreathe time decreases the total amount of time that a crewmember can take to perform an EVA.

9. Prevalence of Cardiovascular Disease in Astronauts

To date, too few astronauts have presented with chronic diseases to perform an accurate analysis of the risk of cardiovascular disease morbidity. Therefore, analyses regarding cardiovascular disease have been limited to cardiovascular mortality. However, interpretations of the data should still be viewed with caution considering how few astronauts there are and how few astronaut deaths are attributable to cardiovascular disease.

In the first study of cardiovascular mortality of astronauts, Peterson et al. (Peterson et al. 1993) examined records from 195 astronauts selected between 1959 and 1991 who participated in NASA's Longitudinal Study of Astronaut Health. Standardized mortality ratios (SMRs) are calculated as the ratio of the number of observed deaths in the astronaut group to the number of deaths expected in a comparison group; a score of 100 is considered to demonstrate consistency between the populations compared. Cause of death in the astronauts was categorized based on death certificate and autopsy reporting, and astronaut death rate was compared to that of the U.S. population, after controlling for age, sex, race, and calendar year. Of the 20 astronauts who died before 1991, circulatory disease accounted for only 2 (10%) of the reported deaths, and the SMRs in astronauts were 47 (95% CI: 5-168) and 64 (95% CI: 7-230) for circulatory disease and ischemic heart disease, respectively. Thus, there were no significant differences between the astronaut and U.S. populations in these comparisons. By far, accidents accounted for the largest proportion of the deaths, with a SMR of 1346 (95% CI: 769-2168). Because these data were from early in NASA's space program, most astronauts were not at an age at which cardiovascular disease may have developed.

A later study of cardiovascular mortality was undertaken to improve upon the validity of previous analyses by comparing findings in astronauts to findings from a matched group of civil servants employed at the NASA Johnson Space Center (Hamm et al. 2000). In a 3:1 ratio of test subjects to astronauts, employees were recruited at the time of each astronaut class. Employees were matched to astronauts by sex, age, and body mass index. Data were derived from physical examinations of active astronauts (required annually), inactive or retired astronauts (voluntary participation), and the matched cohort

(examinations offered every 1-3 years). Cause of death was confirmed by death certificate, with these reports supplemented by autopsy reports in astronauts. Hamm et al. (Hamm et al. 2000) reported no statistical difference in adjusted relative risk of cardiovascular mortality in the astronaut corps. Three of the 195 astronauts and 7 of the 575 comparison subjects had died from cardiovascular disease, which resulted in a relative risk of 1.20 (95% CI: 0.27-5.28). The only difference in mortality between the two groups was for accidental deaths (both occupational and non-occupational), with a reported adjusted relative risk of 22.7 (95% CI: 5.0-104.5). However, there were several potential confounding factors in this study. First, despite best efforts at matching the cohort to the astronauts at baseline, astronauts had a higher educational level (% with graduate degrees) and rate of smoking, and lower mean values of glucose, triglycerides, and hemoglobin, although these latter findings were within clinical normal values. Second, some measures of heart and blood pressure were significantly lower in astronauts than in the matched cohort, although these differences were small and likely not clinically relevant. Factors that could have influenced these results may have been related to lifestyle; lifestyle data was not collected at baseline for the majority of the subjects and only was included in data collection procedures starting in 1994. Third, 11 of the comparison cohort had medical conditions (9 hypertension, 2 diabetes) at baseline that would have been disqualifying factors for astronauts. However, only one of these 11 comparison subjects died during the study period, and analyses excluding these 11 subjects did not substantially affect the outcomes. Finally, whereas physical examinations were conducted by different groups of physicians (astronauts: Flight Medicine Clinic; comparison group: Occupational Health Clinic), clinic tests were performed by the same technicians to ensure the test were performed consistently.

In a follow-on study, Reynolds and Day (Reynolds and Day 2010) searched publicly available records of cause of death for astronauts who were selected for the corps from 1959 to 2004. They determined that the SMR of astronauts dying from circulatory diseases was substantially less than that of the general population. Results were consistent across separate comparison groups, including the population of the United States, Texas, and Harris County (the county in which Johnson Space Center is located). The SMR for astronauts was 27 (95% CI: 9-63) when they were compared to Harris County residents. Lower rates of cardiovascular mortality in astronauts than in the general population likely is related to the extensive medical screening that astronauts must undergo before selection, the frequent re-evaluation of their cardiovascular health that they must undergo throughout their career through annual and flight qualification physicals, and the generally high level of physical fitness that the astronauts are expected to maintain (Reynolds and Day 2010). Interestingly, when similar methodology is used the SMR for death from circulatory diseases in Soviet era and Russian cosmonauts (1960-2013) was SMR 364 (95% CI: 225-557) when they were compared to NASA astronauts (Reynolds et al. 2014). It is possible, however, that the comparisons between astronauts and cosmonauts are not appropriate given that historically cosmonauts have engaged in longer duration missions, through the Salyut and Mir Space Station programs, than NASA astronauts and other culture-related differences in health behavior exist, including alcohol consumption (Shkolnikov et al. 1998). However, interpretation of the results from these particular studies are impaired by issues including lack of control for lifestyle factors (e.g., diet, smoking, alcohol consumption, stress, exercise habits) and

competing risks (e.g., earlier than expected death due to accidents or occupational hazards) (Reynolds and Day 2017).

To date, the vast majority of astronauts have flown only in low Earth orbit where radiation exposures are limited by the protective effects of the van Allen Belts and when in the shadow of the Earth (Cucinotta et al. 2016). Thus, cardiovascular mortality in relation to space radiation exposure can only be assessed in Apollo astronauts who traveled to the Moon. In an attempt to quantify the risks of space radiation for cardiovascular health, Delp et al. (Delp et al. 2016) compared causes of death in deceased Apollo astronauts who had traveled beyond low Earth orbit (n=7) to causes of death for deceased astronauts who flew only in low Earth orbit (n=36), and to causes of death for deceased individuals who were selected as astronauts but never participated in an orbital flight (n=41). The cause of death was obtained from death certificates, official NASA sources, obituaries, or other biographical sources. Similar to findings from previous reports, the proportional mortality rate due to cardiovascular disease was significantly less in astronauts than in the U.S. population of adults between 55 and 64 years old (27%). However, the proportional mortality rate from cardiovascular disease for Apollo astronauts (43%) was significantly greater than rates in both the low Earth orbit astronaut group (11%) and in astronauts who never flew an orbital mission (9%). One strength of this study was the comparison to a group of non-flight astronauts who would be expected to have more similar baseline characteristics to other astronauts than the general population. Otherwise, the work by Delp et al. (Delp et al. 2016) has been widely criticized for its overall methodology as well as its conclusions, which were based on a small number of subjects (Cucinotta et al. 2016).

More recently, Reynolds and Day (Reynolds and Day 2017) applied methods similar to those in their previous reports to calculate SMR due to cardiovascular disease in the Apollo astronauts to address the same question regarding the effects of deep space radiation on cardiovascular mortality. After reviewing records for the same Apollo, low Earth orbit, and non-flight astronauts, Reynolds and Day (Reynolds and Day 2017) reported the opposite conclusions from Delp et al. (Delp et al. 2016), stating that there was no evidence of an increased rate of death due to cardiovascular disease in astronauts who traveled to the Moon. Reynolds and Day (Reynolds and Day 2017) reported that Apollo astronauts have a SMR of 117 (95% CI: 24-343) when compared to individuals who were selected using the same criteria as astronauts but did not fly, and a SMR of 72 (95% CI: 15-210) when compared to astronauts who only flew in low Earth orbit. Further, the SMR of Apollo astronauts (15, 95% CI: 3-43) was lower than that of the U.S. population.

In general, all of this work is limited to computations of mortality risk with no concern for morbidity or the diagnosis of cardiovascular disease. Further, as with all spaceflight studies, the number of spaceflight participants is limited and these participants have had limited total spaceflight exposure. The corresponding level of statistical uncertainty means that definitive conclusions can be drawn only for dramatically large spaceflight effects (Reynolds and Day 2017). A full understanding of the cardiovascular disease risk associated with spaceflight cannot be attained without full participation of the astronaut corps, especially of retirees for whom continued participation in regular physical examinations at the Johnson Space Center or reporting of results to NASA has been voluntary and without specific benefits.

All analyses of cardiovascular mortality reported thus far have a significant limitation. Petersen et al. (Peterson et al. 1993) and Hamm et al. (Hamm et al. 2000) reported higher than expected SMR among astronauts due to accidents or other external causes, which occurred at a younger average age than death due to natural causes. Consequently, it is impossible to determine whether the individuals who died of accidental causes would have developed arrhythmias and cardiovascular disease had they not died at an early age (Austin et al. 2016). No study to date has controlled for competing risks in their analyses. When these competing risks are ignored, the assumption of independent censoring is violated, meaning that those who die at a younger age are not represented in the population who survive. When these competing risks are ignored, the incidence of cardiovascular disease may be overestimated.

The Lifetime Surveillance of Astronaut Health at the NASA Johnson Space Center is currently working to address limitations of previous studies in new analyses of risk of cardiovascular mortality and morbidity. Two new comparison cohorts have been identified (U.S. Air Force Aviators and Cooper Center Longitudinal Study); subjects with more similar baseline characteristics can be chosen from these groups than was possible in previous studies so as to address potential selection bias and healthy worker effects. In addition, larger numbers and more detailed medical records are available for these groups, which should help to control for reporting bias. Information will be drawn from a database of 1.2 million records from the Air Force and from 100,000 participants in the Cooper Center Longitudinal Study. Separate analyses will be performed for each cohort; subjects from each cohort will be selected and matched with individual astronauts in a ratio of 3:1 (cohort: astronaut).

V. RISK IN CONTEXT OF EXPLORATION MISSION OPERATIONAL SCENARIOS

Cardiac rhythm disturbances could jeopardize mission objectives and, at the most extreme, the life of crewmembers. The impact of such an event is related to the mission phase and the individual affected (Hamilton et al. 2005). Clearly, the most catastrophic events would involve the loss of the mission commander or pilot during launch, landing, or course correction activities, particularly in situations in which the crew must function autonomously with little to no support from the ground. Other scenarios that would be particularly serious include a life-threatening arrhythmia during the outbound phase of a Mars exploration mission when return to Earth might not be possible for many months or during an EVA when assistance from another crewmember would be required and care could not be administered until the EVA suit is removed inside the vehicle or habitat (Grigoriev et al. 2009). Under these conditions, other crewmembers would need to treat the affected crewmember using the limited resources and finite supplies available on the spacecraft or in the habitat. While it is assumed that one or more crewmembers will have medical training, it cannot be guaranteed that the affected crewmember is not the physician or crew medical officer.

That there is the potential for a serious medical event to be a concern for exploration missions is illustrated by past events. For example, the incidence of significant medical concerns was calculated to be 0.07 events per person year over an 11-year period on the Mir Space Station. During this 11-year period, there were 30 initial reports of arrhythmias or conduction defects, and 98 reports of recurrence (Goncharov et al. 2004).

Of these, one cosmonaut was evacuated from Mir in 1987 6-months into an 11-month mission, because of a persistent supraventricular tachycardia (Marshburn 2008; Grigoriev et al. 2009), and another cosmonaut received medications for cardiac ischemia during his mission (Marshburn 2008).

D. Primary Prevention (Screening)

To prevent a serious arrhythmia from occurring during a spaceflight mission, selection of astronauts with a low cardiac risk profile could be considered a primary prevention strategy (Hamilton et al. 2005). As an illustration, an Apollo 15 crewmember experienced a myocardial infarction 21 months after the mission during which significant arrhythmias were observed. This raised concerns that the crewmembers should be more carefully screened for occult cardiovascular disease before each mission (Leguay and Seigneuric 1981). Even so, astronauts and cosmonauts have participated in rigorous medical screenings, including those targeted for cardiovascular disease, when selected for training and before launch, yet cardiac arrhythmias and symptoms of ischemia have still been reported during spaceflight (Marshburn 2008).

For ISS crews, each ISS member agency selects and certifies their respective crewmembers using agreed-upon medical requirements and standards developed by the Multilateral Medical Operations Panel. Member agencies then submit their candidates to the Multilateral Space Medicine Board (MSMB) for review; the MSMB is responsible for the implementation of medical selection and crew certification standards, specifically determining eligibility of ISS and visiting crewmembers. Eligibility is determined after in-depth clinical review of all medical data for each potential crewmember, and multilateral consensus is required for certification. Waivers for conditions that are outside of the accepted multilateral standards have been granted in exceptional cases (Bogomolov et al. 2009). While each crewmember is on-orbit, his or her health is monitored by their respective crew surgeon through weekly private medical conferences and periodic health assessments. Status of the crew is discussed each week by teleconference with the Space Medicine Operations Team.

Since the early years of the ISS, perceptions of the cardiovascular disease risk and strategies for screening for cardiovascular disease before a spaceflight mission have evolved. Identification of “several cases of latent coronary artery disease” prompted the reassessment of cardiovascular health screening practices for ISS crews (Bogomolov et al. 2009). Consequently, ISS partners added screening elements including the Framingham Risk Score, high-sensitivity C-reactive protein levels, and electron beam computed tomography or multi-detector coronary angiography. The utility of these tools in an apparently healthy population has been demonstrated. For example, elevated coronary artery calcium scores are associated with increased risk of coronary heart disease, even in asymptomatic men and women (LaMonte et al. 2005). Further, coronary calcium scores have been associated with the degree of stenosis; individuals with CAC scores of 0 have a very low probability (<1%) of stenosis (Haberl et al. 2001). It is expected that adding these elements to the screening will decrease the likelihood that a crewmember will experience an acute cardiac event during a mission that would require immediate care or de-orbiting of the crew, and these tests also will improve the long-term health of the crew. Future screening modalities may provide additional information to protect crews during exploration missions (Romero et al. 2015). For example, it has been

established that some arrhythmias, including atrial fibrillation (Lin et al. 2016), and some cardiovascular disease risk factors are inherited and could be screened genetically.

E. On-Orbit Treatment

Successful treatment of cardiac events that occur during the course of an exploration mission will be wholly dependent upon the skill of the crew medical officer and ground support, if it is available (Gillis and Hamilton 2012). Currently, ISS crews that do not have an assigned physician-astronaut are assigned a designated crew medical officer who receives only 30-40 hours of medical training (Gillis and Hamilton 2012). It has not yet been decided whether an astronaut-physician will be assigned to each exploration mission. Even if crewmembers are sufficiently trained, some barriers may exist to prevent effective diagnosis and treatment of arrhythmias and cardiac events. For example, a crewmember may not want to believe that the symptoms that they are experiencing might be related to a cardiac event because they may be concerned that the medical diagnosis will have a direct and significant impact on the mission (Marshburn 2008). Further, they may be more prone to denial because they believe all pre-existing medical conditions or risks would have been detected during extensive screenings before and during flight. Additionally, Marshburn (Marshburn 2008) has suggested that lower heart rate and blood pressure on-orbit (Fritsch-Yelle et al. 1996a) may result in symptoms of cardiac events developing only during exertion. The adequacy of physical examination also might be affected by background noise in the vehicle (auscultation and ability to hear small changes), and by cephalad fluid shift resulting in jugular venous distension (Arbeille et al. 2001). Although there likely will be an ultrasound machine onboard exploration vehicles to aid in diagnoses, for which the crew would have participated in some familiarization training before embarking on a mission, it is still possible that the crewmembers will not be well versed in all procedures and thus require remote guidance or some form of just-in-time training (Martin et al. 2012).

On-orbit medical care on the ISS includes cardiac specific medications, 100% oxygen supply, and a defibrillator, and presumably similar capabilities will be available for exploration missions. On May 15, 1997, the first defibrillator was launched to the Mir Space Station, and the Space Shuttle and the ISS were also equipped with defibrillators (Marshburn 2008). Cardiopulmonary resuscitation can be performed during weightlessness, but this procedure might be less effective than on Earth because the rescuer would not benefit from their own body weight during chest compressions, which may increase the fatigue rate of first responders. The responder and the patient must be restrained during treatment, and the intravenous delivery system must be specialized because there would be no assistance of gravity in delivery of fluids and medications.

VI. CONCLUSIONS

Although some reports are available, few studies have systematically evaluated the prevalence (or potential risk) of cardiac arrhythmias during short- and long-duration spaceflight. There are several reports of non life-threatening but potentially concerning arrhythmias. Risk factors for arrhythmias, including cardiac atrophy and a prolonged QTc interval, have been reported either during or immediately after spaceflight. Recognizing the potential severity of the mission impact of a serious arrhythmia or other cardiac event, medical screening procedures for astronaut selection and flight assignment have been

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improved. However, it is unclear at this time whether spaceflight and radiation exposures in future exploration missions will contribute to the development of cardiovascular diseases that would impact long-term health of astronauts and cosmonauts.

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VIII. TEAM

Revision Team

Stuart M. C. Lee, Ph.D.: Human Research Program Cardiovascular Discipline Lead; Technical Lead, Cardiovascular and Vision Laboratory, KBRwyle

Michael B. Stenger, Ph.D.: Human Research Program Vision Impairment Discipline Lead; Cardiovascular and Vision Laboratory Manager, NASA Johnson Space Center

Steven S. Laurie, Ph.D.: Human Research Program Deputy Vision Impairment Discipline Lead; Senior Scientist, Cardiovascular and Vision Laboratory, KBRwyle

Brandon R. Macias, Ph.D.: Senior Scientist, Cardiovascular and Vision Laboratory, KBRwyle

Original Contributors

Steven H. Platts, Ph.D.: Head, Cardiovascular Laboratory and Discipline Team Lead, NASA Johnson Space Center

Michael Stenger, Ph.D: Cardiovascular Engineer, Wyle Labs, Johnson Space Center

Tiffany Phillips, BS: Research Specialist, Wyle Labs, Johnson Space Center

Angela Brown, BS: Assistant Scientist, MEI Technologies, Johnson Space Center

Natalia Arzeno, MEng: Biomedical Engineer, Wyle Labs, Johnson Space Center

Benjamin Levine, MD: Director, Institute for Exercise and Environmental Medicine, S. Finley Ewing Jr. Chair for Wellness at Presbyterian Hospital of Dallas, Harry S. Moss Heart Chair for Cardiovascular Research

Richard Summers, MD, Ph.D: Professor, Department of Physiology & Biophysics and Division of Emergency Medicine University of Mississippi Medical Center, Jackson, Mississippi

IX. LIST OF ACRONYMS

DCS	Decompression sickness
JSC	Johnson Space Center
NASA	National Aeronautics and Space Administration
ISS	International Space Station
PAC	premature atrial contraction
PVC	premature ventricular contraction
STS	Space Transportation System
VT	ventricular tachycardia
WETF	Weightless Environment Training Facility